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TUBERCULIN THERAPY IN PULMONARY TUBERCULOSIS.

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Submitted by

Ada Elizabeth Miller, M.B. Ch.B. Edin.

Senior Assistant Medical Officer,

Consumption Sanatoria, Bridge of Weir.

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The renewed interest that has of late been taken in the treatment of Pulmonary Tuberculosis by Tuberculin, as well as the fact that I have been studying the treatment in several cases in the Sanatorium, has led me to bring before you some of my personal observations.

Considering the widespread distribution and high mortality of the disease, and the fact that the general public are every year becoming more enlightened to these conditions, and are eagerly desirous of some permanent remedy, it is only natural that the attention of the medical profession should be directed towards any substance possessing curative properties, and which, even though it may not yet be recognised generally as a cure, suggests the possibility of such.

The hygienic dietetic treatment of consumption has proved of great value especially in early and incipient cases, but judging from statistics it is only a small percentage who are fortunate enough to avail themselves of Sanatorium treatment. Tuberculosis is a disease of the working classes, of whom only a limited number can afford to go into Sanatoriums and reside there three or four months as a minimum. Apart from this, the number of sanatoria in the country is quite inadequate to meet the requirements. Roughly speaking about 5% of cases receive sanatorium treatment. How, then, are the remaining 95% to be treated.

Recently a Tuberculin Dispensary League has been formed for the prosecution of Tuberculin treatment, and

efforts are being made to form dispensaries. In a Special Report to the Borough of Portsmouth, on the Provision of Sanatorium treatment and Tuberculosis Dispensaries, Dr. A. Mearns Fraser, M.O.H. urges strongly that such dispensaries should be given a trial. Besides the Kennington Tuberculin Dispensary in London established by Dr. Camac Wilkinson, others have lately been formed in Street (Somerset), Aldershot, and ~~Gowrie~~ Irvine (Ayrshire). In the Lancet, July 31st, 1909, Dr. Philip reported favourably on the value of Tuberculin in diagnosis and treatment. I venture to bring before you some records of cases which I have treated with Tuberculin. The method I have followed is chiefly that carried out on the Continent, but lately my attention has been directed to the methods of Dr. Camac Wilkinson, whose Tuberculin Dispensary, already mentioned, I had the opportunity of visiting recently. His results are convincing proof of the value of his methods (See "Treatment of Consumption" - Camac Wilkinson).

History.

In the early days of scientific study Sylvius in 1695 was among the first to associate tuberculous nodules with Pulmonary Tuberculosis, and further light was shed on the subject during the period of pathological study at the end of the 18th century, when the belief as to the infective nature of phthisis existed, and attempts at

experimental inoculation were made. Villemin, in 1865, was the first to prove this conclusively. But it was not until the year 1882 that Robert Koch, a health officer in an obscure German town made known his discovery that the disease was caused by a specific organism, thus paving the way for scientific investigations towards the finding of a specific remedy. It had been noted by Merfan,[1] that recovery from a localised focus of disease in the skin or glands seemed to confer immunity against Pulmonary Tuberculosis, thus suggesting to Koch the idea of a specific substance in the Tubercle Bacillus. Koch's discovery of the specific cause of Tuberculosis was followed in 1890 by his exhibition of a specific remedy. Numerous investigations were carried out by him concerning the inoculation of pure cultures of the Tubercle Bacillus in healthy and in tuberculous guinea pigs. The following is a detailed description:-

"When a healthy guinea pig is inoculated with a pure culture of tubercle bacilli, as a rule the wound closes and appears in the next few days to have healed. But in the course of ten to fourteen days a hard nodule appears which soon breaks down and remains until the death of the animal, as an ulcerating area. The course is entirely different when an already tubercular guinea pig is inoculated; the animals best suited for the purpose are such as have been successfully inoculated four to six weeks previously. In such an animal the wound

closes at first, but no nodule develops, and on the second or third day a characteristic change occurs at the site of inoculation, it becomes hard and assumes a dark colour, and this change is not limited to the site itself, but spreads over an area of diameter 0.1 cm.. From day to day it becomes clearer that the altered skin has become necrotic, it is finally cast off, and there remains a flat ulcer which generally heals quickly and permanently, without any infection of the regional lymphatic glands."[2]

This proved that the tuberculous animal, by being previously inoculated, had become immune to such an extent that a further infection had no innocuous effect.

It was further observed that sterilized cultures of tubercle bacilli injected into a tuberculous animal caused death in a short time. Death however did not take place, but improvement obtained if repeated small doses of high dilutions were used.

The chemical analysis of the Tubercle Bacillus has been rendered fairly easy owing to the fact that large quantities of the micro-organisms can be grown on fluid media. Hammerschlag was the first to publish an analysis of the Tubercle Bacillus. He discovered a protein substance in broth and agar cultures which resisted acids.[3] Later Ruppel and Levene[4] examined the decomposition products of this substance and found it to contain a peculiar nucleic acid. This is present in the Bacillus and in its soluble toxins, and is supposed

to contain from 9 to 11% Phosphorus. By further decomposition this nucleic acid is split into Thymin and a neutral substance called Tuberculosin (Ruppel). The action of Tuberculin is ascribed by Von Behring to the Thymin part in the nucleic acid. The toxic nuclein possesses disease producing capacities, and constitutes in all probability the essential endo. toxin of the Tubercle Bacillus. It may be supposed that the various Tuberculins all contain this nuclein substance or its toxic products in greater or less quantity and degree of solubility.

"These laboratory products thus constitute the chief and most powerful weapons we possess in dealing with the stupendous problem of the cure and prevention of Tuberculosis in all its forms."[5]

The first Tuberculin consisted of the products of the growth of the Tubercle Bacillus on broth and was prepared by Koch in the following way:-

Tubercle bacilli were grown on an alkaline veal broth for about six weeks. The bacilli were ~~recovered~~ removed by filtering, and the liquid was evaporated to $\frac{1}{10}$ of its volume. The resulting concentred fluid contained the soluble toxins of the bacilli, and was called Tuberculin (T.). It was presumed by Levene that these toxins contained the decomposition products of the nucleo-proteins, present in the bodies of the bacilli. In

the process of immunization old Tuberculin has no action on the actual bacilli, but only against their toxins.

Koch's next aim therefore was the attainment of immunity against the bacilli themselves. By extraction with decimormal soda he obtained the preparation known as Tuberculin alkalinum (T.A.). This was discarded as it caused suppuration at the site of injection. Finally in 1896 Koch introduced New Tuberculin, which contains the active bodies of the bacilli finely disintegrated, and was prepared in the following way:- Virulent cultures of the Tubercle Bacilli were well dried and ground up in an agate mortar. Normal saline solution was added to the powdered mass and the liquid centrifuged. The upper layer contained the glycerine soluble substances and was analogous to Old Tuberculin (T.A.). This Koch named Tuberculin Obere (T.O.). The deposit was treated again with saline solution and centrifuged, and this process repeated several times. The liquids were then mixed and the resulting fluid was known as Tuberculin Rückstand (T.R.).

In 1901 Koch modified his New Tuberculin and introduced the preparation known as Bacillen Emulsion (B.E.).

This is an emulsion of the Comminuted Bacilli in 50% glycerine, from which the soluble toxins are not removed.

Concerning thespecific action of Tuberculin, Koch believed that it does not kill the bacilli. It acts on living tubercular tissue causing inflammatory changes and necrosis.[6] Tuberculin is an active immunizing agent, that is to say, a reaction takes place in the organism caused by the products of the Tubercle Bacillus, and this leads to the appearance of protective bodies in the serum. In Tuberculin treatment the organism has first to produce anti-bodies - it must prepare its own specific protective substance.

The recent work of Wassermann and Bruck throws some light upon the scientific nature of the Tuberculin reaction. Wassermann's theory is based upon the fact that the reaction depends on the presence of an antibody in the tuberculous tissue, which he calls anti-tuberculin, and an antigen represented by the Tuberculin. The complement which is normally present in the serum, can be appropriated or rendered inert, through the action of the amboceptor or antibody on the antigen. This is known as fixation of the complement. The proof of the disappearance of the complement is shown by the process of haemolysis. If haemolysis is absent, the complement has been absorbed, that is to say, haemolysis only takes place in the presence of free complement. The significance of this depends on the presence of three agents viz. the complement present in the serum, the antibody existing

in thetuberculous tissue, and the antigen represented by the Tuberculin. Wassermann ha s demonstrated the presence of antibodies in the blood of individuals who have been treated with Tuberculin.[7]

Following the announcement of Koch's specific treatment of Tuberculosis, clinical trials were made extensively, but unfortunately the results were far from being satisfactory. Through lack of experience and deficient knowledge in the method of administration and technique unsuitable cases were selected for treatment, and dosage applied without due regard to clinical manifestations. Too far advanced cases were selected for treatment, with the result that some developed general tuberculosis, while in cases of a chronic nature, the disease was rendered active and made rapid progress. It was not thus surprising that Tuberculin fell into disrepute, and there elapsed a period when the general opinion was decidedly against it. Some enthusiastic observers continued its use however and have done so ever since.

Since 1890 Trudean, in spite of opposition, has continuously used various forms of Tuberculin at Adirondack Cottage Sanatorium, principally he says, because success has already been attained in the treatment of other infective diseases, by the production of immunity by the toxic products of the specific cause, and because by similar experiments in animals a certain degree of

success has been attained.[8] He states also that he has formed the opinion that in chronic cases of Tuberculosis, Tuberculin has a favourable influence, that it prolongs life, and that combined with Sanatorium treatment, better results are obtained than with Sanatorium treatment alone.[9]

Various Forms of Tuberculin.

Tuberculin O. Contains the glycerine soluble substances secreted by the Tubercle Bacilli. It is used as a diagnostic agent.

Tuberculin R. This preparation is composed of the actual bodies of the Tubercle bacilli, finely pulverised. 1 c.c. of the original solution is said to contain 10 mgr. of solid substance. Some confusion has arisen with regard to the latter fact, owing to a distinction not being made between the Tubercle Bacilli, and the solid substance derived from the bacilli.

Professor Ruppel[10] has called attention to this fact. I quote from the British Medical Journal,[11] the following accurate account of the method of preparation used by the firm where it is manufactured:-

"1 gramme of Tubercle Bacilli, weighed after drying is rubbed up in the apparatus, and then extracted in 100 c.c. of sterile water. The residue is then centrifuged. The supernatant fluid is collected and labelled T.O. The residue is next dried and powdered,

and again extracted in water. It is then centrifuged, and theresidue is again treated in the same way two or three times. The supernatant fluid of each procedure must not exceed 100 c.c. when mixed together. This is T.R. A given quantity of the fluid is then taken, dried in vacuo and weighed. A small quantity of glycerine and formaldehyde and lastly water are then added, so that 1 c.cm. contains ·002 grammes of dry substance. T.R. is therefore made up to a definite strength, which may be expressed either as 1 c.c. being the extract of 10 mgr. of dry bacilli (100 c.c. being the extract of 1 gramme) or that 1 c.c. contains 2 mgr. of dry substance in solution." It is a mistaken idea therefore to suppose that 1 c.c. of original solution contains 10 mgr. of dried substance. 1 c.c. is made from 10 mgr. of Tubercle Bacilli and contains 2 mgr. of dried substance.

The phial containing the original solution should be well shaken before use. The diluent I use in making the solutions is 20% glycerine in distilled water. The following is the method I have adopted in making the dilutions:-

·1 c.c. original solution ad ·9 c.c. diluent = Sol I = 1 mgr.

·1 c.c. Sol. I ad ·9 c.c. diluent = Sol II = ·1 mgr.

·1 c.c. Sol. II ad ·9 c.c. diluent = Sol III = ·01 mgr.

As an initial dose for an adult I usually use ·001 mgr. This is obtained by taking ·1 c.c. of solution III and adding ·9 c.c. of diluent. For children

I usually commence with ·0001 mgr. obtained in a similar manner. The dilutions are sterilised at 60°C for one hour in order to kill any living bacilli present. I do not usually keep them over a fortnight: they should be kept in a cool dark place.

T.R. may be given in the following ways:-

(a) Continental Method - commencing with minute doses, usually not less than $\frac{1}{1000}$ mgr, and gradually increasing to a maximum dose of 20 mgr, avoiding reactions as far as possible.

(b) English Method - Minute doses of $\frac{1}{20000}$ mgr. are given at intervals of a fortnight and regulated by clinical manifestations, or according to Wright are controlled by the Opsonic Index.

Bacillary Emulsion, New Tuberculin (B.E.). An emulsion of the powdered bodies of Tubercle Bacilli in distilled water with 50% glycerine, the difference between it and T.R. being that in Bacillary Emulsion, the water soluble toxins are not removed. This preparation is said not to be so well tolerated and more likely to cause febrile reaction than T.R. but is supposed to have a higher antipyretic value.[12] 1 c.c. contains 5 mgms. of solid substance. The phials should be well shaken before being used. The diluent I use is ·8% Sodium Chloride and ·5% Carbolic Solution. I prepare the dilutions in a manner similar to those of T.R. with the exception that I use ·2 c.c of original solution to

make solution I (= 1 mgr.) instead of ·1 c.c.

As an initial dose I have used ·00002 c.c. The dilutions are sterilised at 60°C. If carefully prepared they usually keep for several weeks.

Other Modifications of Tuberculin.

Beraneck's Tuberculin (T.B.K.). This preparation was introduced by Professor Beraneck. It should contain all the substances possessing immunising properties, while the toxins which are not supposed to have any immunising properties are left out. It has been highly recommended by some observers especially Sahli.[13] Beraneck considers it less toxic than Koch's preparations.

Broth Filtrate (Deny's) (B.F.). An unheated, unconcentrated filtrate of bouillon culture (filtered through porcelain) of human bacilli. It contains the toxins secreted by the bacilli, and the soluble proteins in the bacilli. It is believed to be a mild form of Tuberculin, and is used to a large extent on the continent.

Von Ruck's Watery Extract. Tubercle Bacilli are powdered and treated with sterilised distilled water, the fat having been previously extracted with ether. The fluid contains pure tubercle proteins.

Landman's Tuberculol. Extracts are made from pulverised tubercle bacilli with glycerine and treated with normal saline. They are separately prepared at the temperature of 40°, 50°, and 100°C. The extracts are then mixed and concentrated in vacuo at 37°C. Good results have been obtained by Continental observers,

by whom it is warmly recommended.

Kleb's preparations are:- Tuberculocidin, Anti-phthisin, Selenin, and Tuberculo-Zozin.

Although the favourable results obtained by Klebs, have not been confirmed by other observers, these preparations are regarded as at least harmless.

Bovine Preparations. These were introduced by Carl Spengler. He holds that the toxins of bovine bacilli are far less toxic to tubercular patients than Tuberculin prepared from human bacilli, and as regards curative action are much superior. Further he concludes that these toxins are antagonistic to each other and that a tubercular patient who is highly susceptible to initial doses of human Tuberculin, should be treated with a bovine preparation.[14] These preparations are prepared similarly to the human ones. They are:-

P.T.O. (Perlsucht-tuberkulin-original) corresponding to T.O.A.

P.T., corresponding to T.A. (T.O.A. evaporated to one tenth.)

P.T.E. Bovine Tuberculin Emulsion corresponding to Tuberculin Bacillary Emulsion.

Dr. Camac Wilkinson states that P.T. is more valuable than P.T.O. especially in cases where the disease is far advanced. He considers it a more powerful immunising agent than any other form of Tuberculin, and that in advanced cases it is less likely to cause febrile or local reaction.[15] In making the dilutions of P.T.O I prepare them in a manner similar to those of T.R. As an initial dose I commence with ·0001 c.c. then ·0005 c.c. and ·001 c.c. successively, and so on.

Methods of Administration.

Various methods have been adopted. These are:-

Subcutaneous.

Oral.

Dermic or percutaneous.

Rectal.

Intravenous.

Intrapulmonary.

Inhalation.

Subcutaneous. This method appears to be the most exact, the most reliable, and the most adaptable. In this way an accurate dose can be administered, the tuberculin being absorbed through the lymphatics unaltered, and unpleasant gastric symptoms are less likely to arise. The most suitable area for injection is the skin of the back between the shoulder blades, alternately on either side, the usual site being about 4 c. from the spinal column from the 7th to the 10th dorsal spines. Here the skin can be more easily raised in folds, is less sensitive and less vascular. The back of the upper arm may also be used as a site for injection, but here there is more liability to a local infiltration. This area however is invaluable in the Dispensary System of treatment. To avoid a local reaction the skin should be well raised, and the needle well inserted into the loose subcutaneous tissue between the cutis and

the fascia. Those into the cutis are more likely to cause infiltration with swelling and redness. According to Carl Spengler, a relation exists between the reaction in the diseased focus in the lung, and the needle track reaction, the reaction at the site of injection thus giving an indication of the severity of the focal reaction.[16] I have occasionally seen swelling and redness with increased tension at the site of injection, accompanied by stiffness and pain in the shoulder. I may mention I have also seen these local signs occur in Phthisical patients after the subcutaneous injection of $\frac{1}{5}$ grain Hydrargyrum Succinimide, but to a much more marked degree. A site should be chosen which is free from induration left after a previous injection; the occurrence of these indurations varies both in individuals and in the form of the tuberculin used.

It is advisable to have the area selected rubbed vigorously with alcohol or ether before the injection, both for the purpose of ensuring asepsis and producing an anaesthetic effect.

Oral. It is impossible to estimate the dose accurately by this method and consequently severe reactions may occur unexpectedly and hypersusceptibility result. Good results have however been obtained by some observers. Dr. Hector McKenzie has given T.R. by the mouth in doses of $\frac{1}{5000}$ mgr., and obtained good effects on the

appetite. Good results were also obtained in the case of tubercular cervical adenitis. In animals it has been proved by experiments that if the vaccine is given on an empty stomach, immunity may be produced.[17]

Latham in April 1908, demonstrated the value of T.R. orally by giving it in doses of about $\frac{1}{2000}$ mgr. at intervals of a week.[18] Tuberculin has also been given per os along with horse serum and promising results have been obtained by Hort and Vere Pearson.[19] Latham exhibited a case of Phthisis before the Royal Society of Medicine, which he had treated with Tuberculin and normal horse serum by the mouth. He gave $\frac{1}{2000}$ mgr. of Tuberculin and 10 c.c. of serum about once a week and obtained good results. The general health of the patient was much improved, the weight increased and the sputum diminished; the fever also was reduced.[20]

I treated 8 patients with T. R. by the mouth. A young woman in the Intermediate Stage of the disease with T.B. in the sputum received 13 doses (·006 mgr.) at intervals, during a period of 5 months. The dose was given an hour before breakfast. There was marked improvement in the general condition, the sputum was nil, no T. B. were found, and the lungs were apparently normal. She was discharged disease arrested. Of the other 7 cases, in 4, both the general and local conditions were improved, in 2 the general condition was improved and the local condition unchanged, and in one there was no improvement.

Dermic or Percutaneous. This method has been employed by Carl Spengler in much debilitated phthisical patients, with fever and hypersusceptibility to Tuberculin, and in children. From one to ten milligrammes of Tuberculin are rubbed into the forearm at intervals of two to four days. It may be accompanied by skin reactions and is undesirable.

Rectal. Suppositories and enemata of Tuberculin have been employed. There exists no indication for this method and according to the researches of Pfeiffer and Trunk, it is completely inactive.[21] The effect of rectal injections were tried by M. Calmette and M. Breton. They were given to four phthisical patients with apyrexia, in the form of an enema consisting of 50 grammes of milk containing ·01 cgm. of Tuberculin. A typical febrile reaction was obtained in all these patients after the injections, proving that absorption of Tuberculin takes place by the rectum.[22]

Intravenous. Koch held that a high agglutinating power indicated a high degree of immunity, and that the agglutinating power could be raised still higher by the intravenous injection of Tuberculin. As it has been proved since, that a high agglutinating value can be obtained by the subcutaneous method, without the production of a reaction, this method has practically been discarded.[23]

Intrapulmonary. This method was introduced by Jacob. The larynx and trachea were anaesthetised, and a catheter

introduced into the opening of a bronchus. It has however proved unsatisfactory.

Inhalation. Tuberculin has been administered in the form of a spray by Kapralik and Von Schroette,[24] the idea being that it had a direct curative action on the diseased focus: The dosage is uncertain, and it employs large quantities of the drug, much of which is probably wasted.

Selection of Patients. The earliest possible application was strongly advised by Koch. It is generally recognised that advanced cases and cases complicated by mixed infection, are unsuitable for treatment. On the secondary processes which are produced by such organisms as the Streptococcus, Staphylococcus, Pneumococcus and Influenza Bacillus, and which occur chiefly in advanced cases, the remedy can have no curative influence, but on the other hand may do harm. In individuals where there is marked debility, where the nutrition is decidedly below par, and when there is extensive softening and cavity formation, tuberculin is contra-indicated. In cases however where the disease is extensive, but the general condition good and provided there are no prominent symptoms, it may be tried but requires special care in administration. Dr. Camac Wilkinson though adhering to the view of Koch's that Tuberculin is incompatible in such cases, reports, that in his experience, if it is applied skilfully and judiciously it may do no harm, and has even seen good results follow the use of it in cases

of severe mixed infection, which had not responded to other forms of treatment and were apparently hopeless.[25] He has also obtained excellent results in cases of Tubercular Laryngitis.[26] As regards elevation of temperature, a persistently high range is a contra-indication. On the other hand where the temperature ranges from normal or below, to 99·4 or 100°F., and where there are no other marked symptoms, and the local condition not extensive, tuberculin may be used. It is said to have an antipyretic action in some cases reducing the temperature to normal.[27] Cases in which the temperature reaches 101° or more, or which rarely fall below 100°, are generally considered unsuitable. Marked shortness of breath or urgent dyspnoea, and a rapid pulse which remains so, after prolonged rest are contra-indications.[28] Haemorrhage is not considered a bar to treatment, but Haemoptysis or coloured sputum, occurring during treatment, demands special care in application. Regarding complications, severe organic diseases are a contra-indication. Among these may be mentioned diabetes, nephritis, and cirrhosis of the liver. Well compensated lesions of the heart are no bar to treatment, but degeneration of the cardiac muscle, or an atheromatous condition of the coronary arteries, necessitates the greatest care in application, or the giving up of it altogether. Epilepsy and marked nervous systoms demand great caution. Pregnancy is not considered a contra-indication. Individuals over

the age of 50 require especial care, as regards cardiac and renal complications. Nathan Raw states that in individuals where there is any localised formation of pus, it is inadvisable to to administer Tuberculin, as there is a danger of dissemination.[29] In this connection I may mention the case of a young woman whom I treated with T. R. (case XVIII). Whether her condition had anything to do with the Tuberculin or not, it is difficult to conjecture, but I should say that regarding patients with fever, which cannot be accounted for by the disease in the lungs, Tuberculin should be exhibited with great caution, and after careful consideration of the patient's condition. Another class of patients to whom Tuberculin may be administered is that in which the disease is one of long standing. When the hygienic-dietetic treatment, change of climate, and other remedies have been tried, and the disease remainds stationary, or progresses very slowly, then the drug may be exhibited.

Mode of Application.

Regarding the large number of successfully treated cases which are on record, the impression gained is that the choice of the preparation is secondary to the mode of application. Careful individualistic treatment is common to all preparations, and no two cases can be treated alike. It is only by the most careful administration, with especial regard to clinical manifestations that one can hope to attain even a small amount of success.

Whichever method is employed all observers agree that severe reactions have no curative action, have no beneficial effect, and as it is possible they may do harm, are to be avoided. Dr. Camac Wilkinson reports that he has never observed any serious effects following well-marked reactions, provided they are not too severe or too frequent. He even says that an occasional reaction with fever is advantageous, especially in the early stages of the disease.[30]

Regarding the method adopted in Germany and on the Continent generally, the principle of application is a gradual increase in dosage, regulated by clinical observations, and the avoidance of reactions if possible. The aim therefore is to attain a high maximum dose without reaction, although it is scarcely possible to avoid a reaction at some time or other during the treatment. The essential points in the technique are, the initial dose, increase in dosage, intervals between injections, and the maximum dose. These vary according to the choice of the preparation used. The more carefully the clinical manifestations are watched, the less likely is it to get a reaction. One of the most important guides regarding the increase in dosage is the observation of the temperature curves. After a rise in temperature following an injection, it is usual to lengthen the interval, and repeat or diminish the dose, according to the degree of elevation. The subjective

symptoms of a reaction must also be taken into account. Trudean finds that reactions take place more readily at doses fixed between ·1 mgr. and 1 mgr., than perhaps at any other stage.[31] An unstable pulse suggests an overdose of toxin, but on the other hand, the quick pulse rate, which is frequently observed in Pulmonary Tuberculosis, due to absorption of the toxins of the Tubercle Bacillus, has been observed to become markedly slower during treatment. A pulse rate of 120 per minute has been noticed to fall to 80 in six months.[32] When a cumulative action or hypersusceptibility is noticed at some period during a course of Tuberculin treatment, as it frequently is, it is assumed there is an increased susceptibility due to too rapid increase in dosage, that is to say, an overdose of the toxin. It may be demonstrated in the following manner:-

A patient has a rise in temperature after an injection. An interval of several days elapses after the temperature has fallen, and the same dose is repeated. This causes a higher febrile reaction than the previous dose. A smaller dose is administered and the patient has again a well marked febrile reaction, thus showing an increasing susceptibility to a decreasing dose of the dose, and suggesting that a cumulative process is taking place. In such a case an interval of a fortnight or longer is made, and a much smaller dose given, and the treatment commenced again with great caution.

As regards the maximum therapeutic dose given, the aim is to obtain the absolute maximum as far as possible in each case, it being recognised however, that the curative effect does not depend on the absolute maximum, but on the relative maximum, that is to say, that size of dose that can just be borne without reaction. When the maximum dose has been reached, it is repeated at increasing intervals, as long as the patient continues to improve. When the absolute maximum is unattainable, the individual maximum dose is repeated several times, and later on, if possible, an attempt made to increase the dose. When the Tuberculin has been discontinued for a time, the next dose given must be reduced accordingly. Regarding the after treatment of Tuberculin treated patients, it is advisable that patients who have been apparently cured, should after a varying length of time, be tested with Tuberculin, and if a positive result is obtained, they should undergo a second course of treatment.

This mode of application applies also to children, the dose of course being smaller. A young child receives $\frac{1}{10}$ and older children $\frac{1}{4}$ to $\frac{1}{2}$ that for an adult.

Opsonic Theory.

A valuable contribution to our knowledge regarding the processes of immunity was made by Wright. Metschnikoff held that practically no phagocytosis took place by the introduction of bacterial elements into a healthy animal,

but that an increase in the leucocytes did occur when the animal had been previously artificially immunized. Further observations proved that during the process of immunization there were found in the blood substances which increased the activity of the white cells. These substances Wright calls opsonins, the word being derived from the Greek word opsono, I cook for table, or prepare pabulum for. He accordingly introduced an elaborate and technical method of determining the opsonic content of a serum to serve as a control in the vaccine treatment of disease. The ratio of the opsonic content of a patient's blood serum to that of a normal individual he termed the opsonic index, and by observations on the presence of a positive and negative phase he regulated the doses of vaccine and intervals between injections. He accordingly employed small doses of T.R. at intervals of one to two weeks.

The method he adopted is the one which I have followed in estimating the opsonic index. The following materials are required:-

Bacterial Emulsion.

Patient's blood serum and normal serum.

White blood cells.

Preparation of the Emulsion. A small quantity of dry killed Tubercle Bacilli is well rubbed up in an agate mortar with a 0·1% Sodium Chloride Solution for about fifteen minutes. The Emulsion is then centrifuged by means

of which clumps are thrown down. A film is then made and examined microscopically and if any clumps are still present, the emulsion is again centrifuged. It is necessary to have the emulsion not too thick; a strength which produces an average count of four bacilli per leucocyte should be aimed at. The emulsion is sterilized at 60° for one hour. I do not usually keep it longer than a week.

Collection of Serum. Three or four drops of blood from the patient's finger are collected in a Wright's V tube. Both ~~sides~~ ends are sealed and the blood allowed to stand for about fifteen minutes before being utilised. The blood from the normal individual is obtained in a similar manner, preferably at the same time of day.

Preparation of White Blood Cells. A few drops of blood from a healthy person are collected in a piece of glass tubing, about four or five inches long, and containing 1.5% Sodium Chloride and .8% Sodium Citrate Solution. Two or three drops of blood at a time are introduced into the tube, and the liquid well shaken up. About 10 to 15 drops are required altogether. It is then centrifuged and the corpuscles are thrown down. The centrifuging should be continued until a distinct white layer known as the "buffy coat" is seen on the top of the red cells. The supernatant liquid is then removed with a pipette, and the corpuscles are washed by adding .8% Sodium Chloride Solution and shaking up. The liquid is again centrifuged,

after which the saline solution is pipetted off, without disturbing the layer of white cells. The latter are then removed with a glass pipette and transferred to a watch glass, and are then ready for use. Fine long drawn capillary pipettes are then taken and marks are made with a grease pencil about ¾ inch from the ends. Each pipette is numbered according to the serum. A quantity of white cells are drawn up and the whole mixed on a slide. Finally the whole is drawn into the pipette and sealed, each serum being done in a similar manner. The pipettes are then placed in an incubator for 15 minutes and when taken out the contents are mixed thoroughly on a slide. A drop of the liquid is placed on a clean slide, and a film prepared by drawing one slide across the other. Two films are made from each serum. For fixation I use Formalin for about one minute. I stain the slides in the following way:-

The films are placed in Haematoxylin for an hour or two, as by this the protoplasm is well demonstrated. They are then stained with Carbol-fuchsin, washed in water and decolorised with Methylated Spirit. Following this anilin hydrate 2% and again Methylated Spirit. Finally the films are well washed with water and counter-stained with 1% Methylene Blue for about 15 seconds.

Recent attempts at shortening the technique of the tuberculo - opsonic index have been made by using

emulsion of organisms which have previously been stained with carbol-fuchsin. The majority of observers agree that accurate results cannot be obtained by this method.[33]

The chief difficulties I find in the technique are the preparation of the emulsion and the making of the films. Experience alone teaches the required strength of the emulsion. The thickness of the film depends to a large extent on the angle of the moving slide to the stationary one, and upon the presence of the moving one. I have several times found the leucocytes are collected at one end of the slide, and none to be found elsewhere, while at other times I have got any amount of leucocytes scattered over the film, but the cells appeared crinkled, and the protoplasm very irregular. On other occasions I have noticed the white cells to be very small in size, the protoplasm being greatly diminished, which I suggest may probably be due to over-fixation in formalin. It is important also that the centrifuge should run without vibration, as otherwise the phagocytes may be disintegrated. The leucocytes should be separate from each other and clumps of cells should be avoided. I generally count 100 cells, as I do not think less will give accurate results.

Wright's investigations represent an elaborate and brilliant work, and he has had many enthusiastic followers. He has himself obtained marvellous results in cases of localised tuberculosis viz. lupus, tubercular

ulcers, and glandular swellings in the neck.[34] The task however in Pulmonary Tuberculosis has proved more difficult and unsatisfactory. The value of the method in this condition is limited owing to the wide variation of the index. In advanced cases the fluctuation is marked, the index varying from 0·3 to 1·8 or higher. Most observers agree that the only cases which can derive benefit from the treatment are those classed as chronic, and possibly in early cases where the index is below normal. Dr. R. W. Philip has stated that he cannot accept the opsonic index as a reliable guide to the progress of immunisation and that he found the opsonic curve often gave indications antagonistic to the clinical signs and symptoms.[35]

But apart from the limited value of the index in Pulmonary Tuberculosis, other considerations lead to the conclusion that Wright's method is inapplicable in many cases in the treatment of disease. The difficulty in obtaining a standard index may be considered an obstacle to the finding of accurate results. Observations were made here with special reference to this point. The normal index is stated to vary between ·8 and 1·2. If the standard remains constant from day to day, then the variations in the patient's index can be relied upon. Assuminghowever that the normal is at a different level each day, then the results will vary accordingly, and

if this is so, can the indices obtained be regarded as accurate! A pool serum of three healthy individuals was taken as a standard, and against this, the indices of healthy individuals were taken on several successive days. The results do not appear satisfactory; the indices varied each day, In the case of M.A., the index on seven successive days ranged between 0·6 and 1·3: in the case of C.A. it ranged between 0·95 and 1·44. Again in the cases of J.G., E.G. and A.M., the index varied from ·5 to 1·4, ·7 to 1·3, and ·6 to 1·7 respectively, as taken against a pool serum of these three. Taking these indices of healthy individuals and comparing them from day to day with the patient's index, it naturally follows that the patient's index will vary accordingly, and if this is so, how can the results be considered accurate? This I consider a source of error, which lowers the practical value of the method. Other observers have found that on repeating the counts of the same pair of slides an absolutely different index was obtained.[36] Further the elaborate and complicated technique, the amount of time, skill, and experience required to carry it out, renders the method valueless in many cases as a clinical guide. To the majority of general practitioners who aim at specific treatment in combating such a widespread disease, laboratory methods are inapplicable.

It has been stated that infants do not apparently depend on opsonins for their bacterial defence, as they often thrive on an index of ·01.[37]

I have made observations on the indices of a few patients having Tuberculin treatment. The injections were given at intervals of two weeks. Two of the cases J.F. and H.H. were in the early stage (Turban) of Pulmonary Tuberculosis, the disease in both being quiescent. In three cases J.S., C.G. and J.B. the disease was also inactive.

The following are the records:-

Date,	J. Scobia.	C. Graham.	H. Henderson.	
April 13th, '09.	1.09	1.4	.93	100 cells counted.
April 13th, '09.	.008 T.R.	.001 T.R.	.001 T.R.	
April 14th, '09.	.98	.94	.84	"
April 15th, '09.	1.1	1.8	----	"
April 16th, '09.	1.08	1.3	1.3	"
April 19th, '09.	.98	1.4	1.02	"
April 20th, '09.	.89	.95	.83	"
April 21st, '09.	1.39	1.88	1.41	"
April 22nd, '09.	1.38	1.3	1.31	"
April 23rd, '09.	1.02	.82	1.08	"
April 26th, '09.	.94	.85	.6	"
April 27th, '09.	.85	1.14	.79	"
April 28th, '09.	1.5	.97	1.2	"
April 28th, '09.	.008 T.R.	.001 T.R.	.001 T.R.	
April 29th, '09.	1.43	1.42	1.47	"
April 30th, '09.	1.15	1.25	1.17	"
May 3rd, '09.	.69	.93	.88	"
May 25th, '09.	.96	1.1	.64	"
May 26th, '09.	.008 T.R.	.001 T.R.	.001 T.R.	

May 27th, '09.	.77	1.01	1.01	"
June 1st, '09.	1.1	.84	.96	"
June 8th, '09.	.79	1.07	.92	50 cells counted.
June 10th, '09.	.008 T.R.	.002 T.R.	.002 T.R.	
June 11th, '09,	1.06	1.1	.85	100 cells counted.
June 23rd, '09.	.5	1.3	.9	25 cells counted.
June 24th, '09.	.009 T.R.	.003 T.R.	.002 T.R.	
June 25th, '09.	----	.65	.63	

Date.	J. Brunton.	J. Fernando.
May 25th, '09	.21	.78.
May 26th, '09.	.001 T.R.	.001 T.R.
May 27th, '09.	.89	
June 1st, '09.	.94	.76
June 8th, '09.	1.1	
June 10th, '09.	.001 T.R.	.001 T.R.
June 11th, '09.	1.1	1.1
June 23rd, '09.	1.9	1.3.

Clinical Trials.

The preparationswhich I have used as therapeutic agents are Tuberculin R, and to a less extent Bacillary Emulsion. I am also treating some cases with the bovine preparation, P.T.O. Some of the cases in whom the diagnosis was undecided were tested before treatment with T.O., in all of whom the result was positive.

The patients selected were all in the Early or Intermediate Stage (Turban) of the disease, with the exception of one advanced case.

Regarding the method of administration the majority of patients were treated according to the Continental Method, using small doses, increased gradually; eight cases received T.R. by the mouth, and five were treated according to the old English Method, receiving small doses subcutaneously at intervals of about a fortnight. Three of the cases treated were complicated with Tubercular Laryngitis; four cases showed the following complications respectively:-

Tubercular Enteritis and Albuminuria, Appendicular Colic, Recurrent Haemorrhage and Rheumatism.

When given subcutaneously I administer the dose between 9 and 10 a.m. As a general rule I give the injection into the interscapular region, and in several cases have obtained a local reaction, the chief signs of which are redness, swelling and induration. After several injections have been given, these local reactions

very often cease. Some individuals are much more susceptible than others, in many there being no indication of a local reaction, while in others the signs are marked after every injection. I have used the back of the forearm as a site, and have formed the opinion that, in this area, there is more danger of a local reaction.

Initial Dose. As a general rule I usually commence with .001 mgr. T.R. In six cases I gave .01 mgr. T.R. as an initial dose, with the following results:-

Case I. Did not react until .7 mgr. was reached, when there was a slight reaction.

Case II. No reaction until .2mgr. The reaction was marked.

Case III. Slight reaction at .03 mgr: occasional slight reactions after this. I had well marked local reaction.

Case IV. Slight reaction at .4 mgr; appeared to be very tolerant.

Case V. Marked reaction to initial dose and appeared susceptible even to smaller doses.

Case VI. Reacted slightly to initial dose, and on this being repeated had a marked reaction.

I think it advisable to commence with a dose not larger than .001 mgr.

Rate of Progression. Progression in dosage varies according to the susceptibility of the individual, some

patients being able to reach fairly large doses in a comparatively short time, while in others when the dose has to be decreased and the intervals lengthened, the time required is much longer.

Reactions. A feature which has presented itself forcibly to me during the treatment, is the varying susceptibility to the drug in different individuals, and this fact emphasises the statement that there can be no routine method, and that each patient must be treated on his own ~~methods~~ merits. I have seen reactions appear at all stages in dosage between .001 mgr. T.R. and 6 mg. T.R. In one case I gave up to 5 mgr. T.R. without obtaining any reactions; following this 6 mgr. was given, and the patient reacted to 102°F. Other two cases did not react until 2 mgr. was reached, when they both reacted to 102°F., while others have reacted to minute doses, viz:- .001 mgr. and .008 mgr. The character of the reaction varies in different individuals. There may be fever without any other symptoms, or it may be accompanied by general constitutional disturbance, such as shivering, headache, pains in the limbs, nausea, and less commonly vomiting: or the reaction may be a local one, occurring at the site of injection and indicated by the cardinal signs of inflammation, or in the focus of disease in the lung, indicated by increased cough, expectoration and sometimes pain in the chest. One patient (case VIII) after a dose of 2 mgr. T.R. had a marked febrile reaction, and showed all the classical

symptoms of a typical reaction. I have observed other cases have definite subjective symptoms without any rise in temperature. One woman after .005 mgr. T.R. complained of headache, shivering and vomiting, but showed no elevation in the temperature curve.

The reaction may be short or prolonged. In the former, the temperature falls usually in about 48 hours, and in the latter the evening temperature remains elevated for several days with a morning remission, and gradually diminishes. The majority of reactions I have had to deal with have been short in duration, the temperature returning to normal the following day. The time at which the reaction most commonly occurs, I have noticed to be between 12 and 24 hours after the injection. I usually keep the patient in bed the following day; if below 101°, I allow him to "rest out" part of the following day, unless there are marked subjective symptoms. For severe headache spirit lotion applied locally, and Codeinae Syrup internally are suitable remedies. The symptoms of a reaction however usually disappear the following day without any treatment.

Maximum Dose. I have not been able to proceed further in dosage than 6 mgr. T.R. as the patient has either left the Sanatoriumor intolerance is produced at this stage, and it has not been thought advisable to continue the treatment. In some cases I could not give more than 3 mgr. T.R. on account of apparent susceptibility.

Length of Time. In treating Sanatorium patients it is difficult to carry out a complete course of treatment, as many of the patients do not remain longer than 3 or 4 months, and 5 or 6 months at least is the time required. I gave up to 6 mgr. T.R. to one Sanatorium patient in 3 months; this patient however showed exceptional tolerance, having no reactions until that was attained

In 8 cases during treatment I have observed the appearance of coloured sputum. I cannot say whether this fact has anything to do with the Tuberculin or not. As an unusual accompaniment of a reaction, I may mention one case, in whom there was an enlarged axillary gland.

Attention has been drawn to the albuminuria accompanying a reaction. I have had the urine examined after an injection in ~~the~~ 40 instances, in all of which the temperature was 100°F or above. In one of these a trace of albumen was found.

Regarding various factors influencing a reaction, I consider the presence of gastric disturbance, transient fever, coloured sputum or pleurisy, is a contra-indication to a dose, it being wiser to delay the administration until these symptoms have subsided. A continued loss of weight I regard as an indication to postpone the administration.

I examine the chest condition at intervals during the treatment.

Reference has been made by Carl Spengler[38] to a special method of staining sputum, by which the protoplasm of the leucocytes is better demonstrated, thus enabling the bacilli to be distinguished as intracellular or extracellular. He states that in Tuberculin treated cases, when the bacilli are intra cellular, the prognosis is favourable, and that it is unfavourable when they are extracellular. The method of staining is as follows:- The sputum is spread thinly on a slide and stained with Carbol-fuchsin. It is decolourised with an alcoholic solution of Rosolic Acid, and a drop of water added. A drop or two of an alcoholic solution of Malachite Green is then applied for about half a minute, and the film washed in water. The nuclei are stained pink by theRosobic Acid and the protoplasm is stained green by the malachite green. I have examined the sputum of some Tuberculin treated cases by this method, but have not obtained conclusive results, the bacilli appearing to be both intra-cellular and extra-cellular on the one slide.

Cases.

Case I.

F. M. Female: aet 17: Stage Int. (Turban) Sputum ∂r. XVI: T.B.+ General condition good.

T.R..0005 .003 .005 .007 .01 .02 .04 .06 .08 .09 .1 .3,

no reaction. .5 mgr. slight reaction 100°: .7 100.2°: .7 99.8°;

.7 .7 .8 .9 1 mg. 2 mg. no reaction.

3 mgr. 99.2 headache: 4 mgr. 100.2°: 4 mg. 101.8° headache, shivering, general malaise.

2 mgr. 101° 2 mg. 101.2° headache, nausea.

No. of injections = 27: Time = 5½ months: maximum dose = 4 mg.

Sputum = ∂r. IV. T.B. General condition much improved: L.C. apparently unchanged. Discharged feeling very well.

Case II.

S.C. Female aet 22. Stage early. Sp. =hXXVIII. T.B.+ G.C. Fair.

T.R. .001 mgr. .003 .005 .007 .009 no reactions.

.02 100.6° sickness, pain at site of injection.

.02 100.4° sickness, malaise, anorexia.

.005 .006 .007 .008 .009 .01 .03 .05 .07 .09 .1 = 1.2. no reactions.

3 mgr. 100.2° headache, pain in chest: .1 mgr. 99.2° : no subjective symptoms.

.2 .3 .4 .6 .8 1 mgr. 2 mgr. no reactions.

3 mgr. 100.2° headache, nausea, shivering.

2 mgr. 3 mgr. 99.8°: 3 mg. 101.8° nausea: 3 mgr. no reactions.

No. of injections = 34: Time = 6½ months; maximum dose = 3 mgr.

Sp. = ~~gr~~. II. T.B. nil (after 23 examinations).

G. C. markedly improved. L.C. Disease arrested.

Feels very well.

Case III.

J. P. Female aet. 22: Stage Int.: Sp. = ~~gr~~. VIII: G. C. fair: T.B. numerous.

Evening temperature = 98.4° to 100°F:

Pulse = 88-104.

T. R. .001 mgr. .003 .005 .005 .007 .009: no reactions.

.02 .04 .06 .08 .1 .3 .4: no reactions.

.6 .8 No reactions.

1 mgr. shivering: 2 mg 99.6°: 2 mg. 2 mg. 99.6°:

2 mg. no reaction.

3 mgr. 100° shivering, headache: 3 mgr. 100.2°

2 mgr. 100.4°: 3 mg. 101.6° shivering.

Apparent intolerance at 3 mg.

No. of injections = 23: Time = 4½ months: maximum dose = 3 mg.

Sp. = ~~gr~~. XVI: T.B. = a few: G.C. improved: L.C. improve

Temperature = normal: pulse 76 to 96. Feels very well.

Case IV.

A.M. Female aet. 23: Stage Early: G.C. Fair: Sp. ~~gr~~. III: T.B. a few.

T. R. .001 mgr. .003 .005 .007 .009 .01 .03 .05 .05 no reactions.

.07 101.2°: .01 .02 .04 .06 .08 .1 no reactions.

.2 99.8° shivering, nausea, headache: .4 100.8° nausea.

.2 shivering, headache: .2 101.2° headache; complained of not feeling so well, and treatment was discontinued for about 3 weeks.

.2 100.6° shivering: .1 101.2°: .1 no reaction: .2 shivering, headache.

Apparent intolerance at .2 mg.

No. of injections = 24: Time = 5 months: maximum dose = .4 mg.

Sp. = ♂r. II: T.B. : G.C. improved: L.C. improved - quiescent condition. Feels very well.

Case V.

P. T. Male aet. 20: Stage early: G.C. fair: Sp. ♂r. VI: T.B. large numbers.

T. R. .001 mgr: .002 .004 .006 .01 .03 .05 .07 .09 .1 .2 .3 .4 .5 .7 .9 1 mg. 2 mg. no reactions.

3 mgr. shivering: 4 mgr. shivering: 5 mgr. 100.4° general malaise: 1 mgr. malaise: 1 mgr. 100.4° malaise.

Apparent intolerance at 5 mg.

No. of injections = 23: Time = 4 months: maximum dose = 5 mg.

Sp. = ♂r. V: T.B. = a few: G.C. poor: L.C. unchanged. Lost weight: Discharged, not feeling well. Died 3 months after discharge.

Case VI.

N. M. Male aet. 29. Stage Int: Sp. = ~~dr~~. XXVIII:
T.B. several: G.C. fair.

T. R. .001 mgr. .002 .004 .005 .006 .008 .01 .03 .05
.07 .09 .1 .3 no reactions. .7 101° general
malaise: .5 malaise.
.5 .7 .9 no reactions: 1 mgr. 100° shivering,
malaise, rapid pulse. .9 sickness, vomiting, malaise:
9 100° malaise.
Apparent intolerance at 1 mg.
No. of injections = 21: Time = 5½ months: max.
dose = 1 mg.
Sp. ~~dr~~. VII: T.B. one or two: G.C. much improved:
L.C. improved: Discharged May 1910 feeling very
well indeed. October 1910 - keeping very well.

Case VI.

J. H. Male aet. 23: Stage Int. T.B. : G.C. poor.

T. R. Received 17 injections. .001 mg. to 1 mg. Reacted
to .8 and to 1 mgr.
G.C. improved: L.C. unchanged: T.B. : Discharged
feeling very well.

Case VII.

J. S. Female: aet. 21: Early: T.B. : G.C. poor.

T. R. Received 10 injections. .01 mg. to 6 mg. in 4
months. Slight reactions. Was losing weight and
apparently did not seem so well.

Case VIII.

J. S. Male: aet. 17: Stage early: L.C. - Slight dulness a few crepitations at right apex.

Sp. and T.B. nil. History of cough, loss of appetite and flesh and coloured sputum.

T.O. = 1 mgr. = local reaction 100.6°.

T. O. =1 mg. = slight reaction 99.2°.

T.O. = 2 mg. = Reaction 100°. Diagnosis = Pulmonary Tuberculosis.

T.R. Received 20 injections in 2½ months = .001 to 1 mg. no reactions.

2 mg. 101° headache, shivering, vomiting.

2 mg. 101° headache, shivering.

Sp. nil. T.B. nil. G.C. good.

L.C. no abnormality, except slight impairment in resonance at right apex.

Discharged disease arrested - feeling very well.

Case IX.

J. M. Male aet. 30: Int. T.B. : G. C. fair.

T. R. Received 22 injections in 3 months. .001 mg. to 5 mg. No reactions. 6 mg. 102° shivering.

6 mg. 100° shivering.

L. C. unchanged: G.C. not very satisfactory: Treatment discontinued.

Case X.

R. G. Male aet. 24: Early: T.B. : G.CC good.

T. R. Received 21 injections in 3½ months. 1001 mgr. to 2 mg. moderate reactions. G.C. improved. L.C. very little detected. T.B. present. Discharged feeling very well.

Case XI.

B. M. Male aet. 20. Int. T.B. : G.C. fair.

T. R. Received 16 injections in 4½ months. .001 mg. to 1 mg. Slight reaction to 1 mg.

L.C. unchanged - G.C. improved. T.B. : Discharged July'10, condition fair. Treatment continued at dispensary outside. Received up to 4 mg. T. R.

Case XII.

G. W. Female aet. 29: T.B. nil: Nothing detected in chest: G.C. good.

History of cough, pleurisy and haemoptysis.

Received 1 mg. T.O. no reaction.

2 mg. T.O. no reaction: 5 mg. T.O. 102°, shivering, sickness, vomiting. Diagnosis - Pulmonary Tuberculosis.

T.R. Receive 8 injections in 5 weeks: .001 mg to .007 mg: appeared to be susceptible to small doses.

Case XVIII.

J. H. Female aet 20: Early. T.B. : G.C. fair.

T. R. Received 14 injections. .001 mg. to .07 mg.: no reactions up to .1 mg. .3 mg. 101.4°: .1 mg. 102.6°: .05 .07 - no reactions. T.R. was discontinued as evening temperature became slightly higher and pulse rate more rapid. L.C. appeared to be improving. A few weeks after T.R. was stopped. Patient developed pelvic peritonitis and was operated on for pyosalpinx. Died 4 days after operation.

Case XIX.

B. M. Female aet. 22. Int. T.B. : G.C. fair.

T. R. Received 19 injections .001 to 3 mg: few reactions. Temperature more fluctuating. G.C. good: L.C. unchanged: T.B. .

Case XX.

Mrs. S. aet. 31. Int. T.B. : G.C. poor.

T. R. Received 8 injections. .01 mg. to .1 mg. no reactions: .2 mg. 102.4° shivering, headache, gen. malaise. Appeared to be doing well but had to leave Sanat. because of domestic reasons.

Case XXI.

L. N. Female aet. 17. Int. T.B.present, G.C. fair. Suffered from Rheumatism.

T. R. Received 15 injections in 2 months. .001 to .09 mg. No apparent improvement.

Case XXII.

Mrs. C. aet. 48. Int. T.B. : G.C. fair. Tubercular Laryngitis.

T. R. Received 23 injections in 4½ months. .001 up to .02 mgr. no reaction. .03 mgr. marked reaction. 103° malaise, vomiting, headache. This dose was given during menstruation: .03 .05 .07 no reaction: up to .8 mgr. Moderate reactions: Gen. condition improved: L.C. unchanged.

practically unchanged. T.B. : Discharged condition fair. T.R. continued at Dispensary outside - now on B. E.

Case XXIII.

R. M. Male aet. 34. Stage early. T.B. : G.C. fair.

T. R. Received 11 injections in 1½ months. .001 to .1 mg. No reactions. G. C. improved. L.C. improved. T.B. nil.

Case XXIV.

T. G. Male aet. 20. Early. T.B. nil. G.C. good. Very little detected in chest. Had attacks of appendicular colic before admission.

T. R. Received 10 injections in 2 months. Reacted to initial dose and complained of some abdominal pain. .01: was then given .005 to .01 mg. several reactions. Appeared susceptible to small doses. G. C. good: practically nothing abnormal in chest.

Case XXV.

H. C. Male aet. 38. G.C. fair. L.C. suspicion of dulness at left apex and suspicion of few creps in right lung. History of Bronchitis since childhood, cough and expectoration, night sweating, coloured sputum and loss of flesh.

T. O. 1 mgr. - pain in side, no rise in temperature: 2 mg. 99.6. 5 mgr - 100.2° shivering, headache. Diagnosis = Pulmonary Tuberculosis.

T. R. Was apparently doing well but had to leave the Sanatoria. G.C. improved: L.C. apparently normal.

Case XXVI.

R. M. Male aet. 21. Stage early. G.C. fair. Chronic

diarrhoea and Albuminuria.

.005 to .1 mg. no reactions - practically no change in condition.

Case XXVII.

J. M. Male aet. 18. Stage Int. G.C. poor. T.B. : Tubercular Laryngitis.

B. E. Received 18 injections in 2 months. .00002 c.c. to .004 c.c. No reactions: Temperature improved. T. B. : G.C. improved: L. C. improved. Throat practically unchanged.

Case XXVIII.

J. G. Male: Stage early: Recurrent Haemorrhage.

T. R. Received 8 injections. .0005 to .006 mgr. at fortnightly intervals: no reactions. L. C. improved: G. C. satisfactory: c.sp. during treatment. Discharged feeling very well.

Case XXIX.

J. S. Male aet. 35. Stage Int.

T. R. Received 10 injections. .006 to .009 mgr. at fortnightly intervals: No reaction. L. C. improved: G. C. improved. T.B. present. Moderately well.

Case XXX.

C. G. Male aet. 22: Stage Int: T.B. .

T. R. Received 8 injections. .001 to .004 mgr. at fortnightly intervals. G.C. improved. Discharged. Had Pleurisy 3 months after discharge: Slight Haemorrhage 11 months after: died 10 days after Haemorrhage.

Case XXXI.

H. H. Male aet. 17: stage early.

T. R. Received 6 injections .001 to .003 mgr. at fortnightly intervals: No reaction. G. C. improved. T.B. present. L.C. unchanged. Re-admitted 11 months later in advanced stage of disease.

Case XXXII.

M. G. Female aet 21: Stage Adv: G. C. fair.

B. E. Received 17 injections in 2 months .0000005 c.c. to .001 c.c. - No apparent improvement: thought advisable to discontinue Tuberculin.

Case XXXIII.

Mrs. B. Female aet. 27: Stage Int: G. C. poor.

T. R. Received 9 injections .0005 mgr. to .008 mgr. Reacted to .008 mg. 102°: .006; No reactions. .008 102°: reactions were prolonged in character. Did not appear to be doing well: T.R. discontinued.

Summary.

Reviewing the foregoing records of cases, it cannot be said that any very striking results are obtained. Several of the cases appeared to do well, while others showed no apparent improvement.

It is possible the method of administration is at fault, and probably were larger doses aimed at, a higher degree of immunity might be attained.

In the early and intermediate stages of Pulmonary Tuberculosis, Tuberculin has proved to be of value, but as all the cases I have treated were Sanatorium patients, it is difficult to say to what extent the hygienic-dietetic element in the treatment is responsible for improvement gained.

In order to carry out the treatment successfully, extreme care and skill are required, as well as an accurate knowledge of the subject, which can only be acquired by experience.

The treatment can be carried out by observations of clinical manifestations, without the aid of the Opsonic Index. In Pulmonary Tuberculosis, the Opsonic Index as a guide in controlling dosage, is practically valueless.

Although Tuberculin has not yet been adopted by the medical profession generally as a means of cure, it has great future possibilities. Assuming that it can be relied upon as a definite curative agent, the system of treating patients at Tuberculin Dispensaries,

would certainly be beneficial to the working classes.

It is available for the masses, is economical, and can be carried on while the patient continues his daily work. Though Sanatorium treatment is of great value in the early stages of the disease, the "working consumptive" is reluctant to give up his means of earning a living, and ~~to~~ go and reside in a Sanatorium for several months, and consequently the disease remains undetected, and may not be discovered until it is in an advanced stage. By treatment with Tuberculin at a dispensary, the patient can still provide for his family, and the disease is therefore much more likely to be detected in an early stage.

By this method the diagnostic use of Tuberculin can also be exhibited.

The establishment and carrying on of Tuberculin Dispensaries would incur considerable less expense, than the erection and upkeep of Sanatoria, and a much larger percentage of patients could be treated.

I cannot conclude without referring to the lamented death of our great authority on Tuberculin, Professor Koch, on whose discovery and scientific investigations, this thesis is based, and expressing the hope that his efforts may yet be crowned with success.

I have to thank Dr. Guy, the Medical Superintendent, for permitting me to record the cases, and for his kindness in affording me every opportunity for carrying out my investigations.

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Explanation of Abbreviations.

Int. - Intermediate.

Sp. = Sputum.

℥r. = ~~Gramme~~. Drachm

Mg. or mgr. = Milligramme.

L.C. = Local condition.

G.C. = General condition.

T.B. = Tubercle Bacilli.